A network-based signaling mechanism of cancer development and progression

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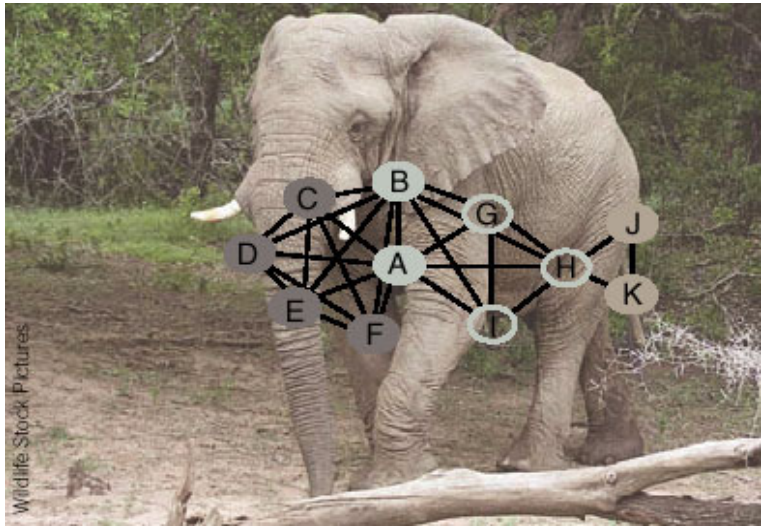
Our challenges: getting insights from data

High throughput technologies drive modern biology.

Huge amount of biological data have been generated.



The bottleneck to achieve this goal is no longer a lack of data, but the lack of *ingenuity and computational means* to integrate knowledge and high-throughput data.

Roles of computational biology

- Data are more comprehensive and unbiased, however, 'real signals' are buried in flood of data.

- By integrating these data, we could ***ask inspiring and fundamental questions (bio), develop elegantly computational methods (compute/stat/math) and lead to new insights (bio) into old data.***

- More importantly, we could ask questions from a unique angle ***– considering biology and computation in an integrative manner.***

- Insightful results in turn lead to ask new questions and design wet-lab experiments.

Cancer gene mutation, tremendous complex?

- Genome-wide sequencing of tumor genomes have revealed tremendous diversity and little overlap of causally mutated genes between individual patients' tumors, even for tumors of the same tissue origin.


CANCER

First Pass at Cancer Genome Reveals Complex Landscape

8 SEPTEMBER 2006 VOL 313 SCIENCE www.sciencemag.org

Is that hopelessly complex?

Tumor genome sequencing, useless?

LETTERS

edited by Etta Kavanagh

Limits to the Human Cancer Genome Project?

9 FEBRUARY 2007 VOL 315 **SCIENCE** www.sciencemag.org

It is time- and resource- consuming with unclear results?

Cancer and cellular signaling

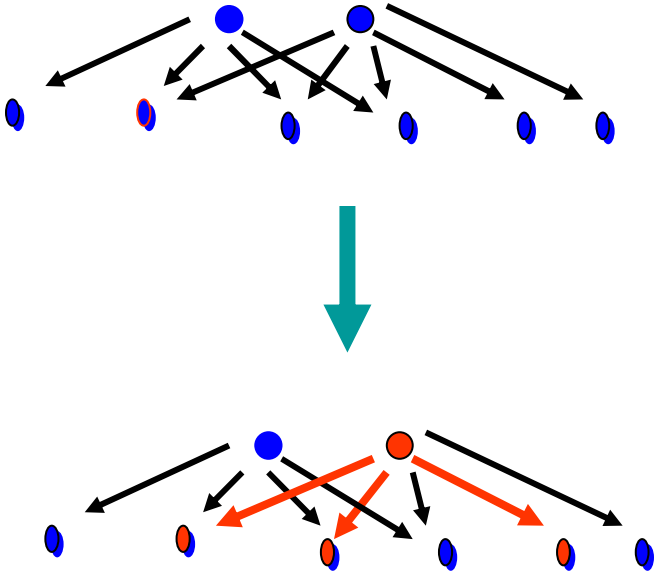
- Cells use sophisticated communication between proteins in order to initiate and maintain basic cellular functions such as growth, survival, proliferation and development.
- Alterations of cellular signaling events, such as those that arise by mutation or methylation, can result in tumor development.
- Cancer driver mutation: the mutated genes drive the rampant cell growth that causes cancer
  - **Oncogene:** prompting the onset and development of cancer.
  - **Tumor suppressor gene:** protecting a cell from one step on the path to cancer.
  - **DNA methylation:** a type of chemical modification of DNA that leads to gene silencing.

Questions on signaling and cancer

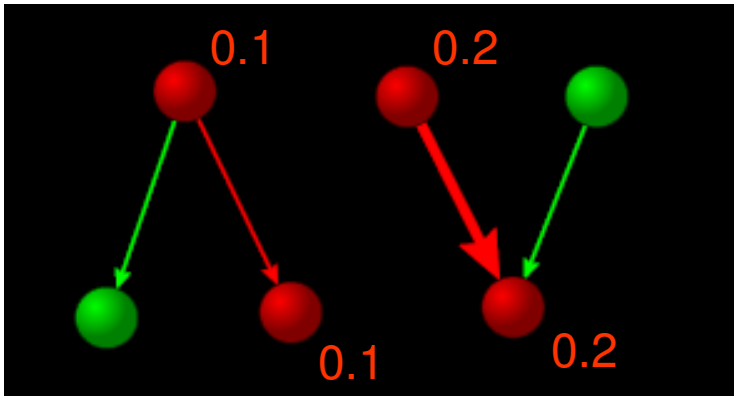
- Enormous efforts have been made over the past few decades to illustrate cancer signaling. However, it has been a struggle to get clues:
  - How cancer signaling is structurally and functionally organized?
  - Where the oncogenic stimuli are embedded in the network architecture?
  - Is any driving signaling event, 'oncogenic signaling addiction' (the signaling event is frequently used by cancer cells)?
  - What are the principles of triggering oncogenic signaling events by genetic and epigenetic alterations?
  - Are there any signaling partnerships generally used to generate tumor phenotypes?

Oncogenic signaling, gene mutation and methylated gene silencing

Normal cellular signaling



Cancer signaling: red nodes represent cancer mutated or methylated genes.



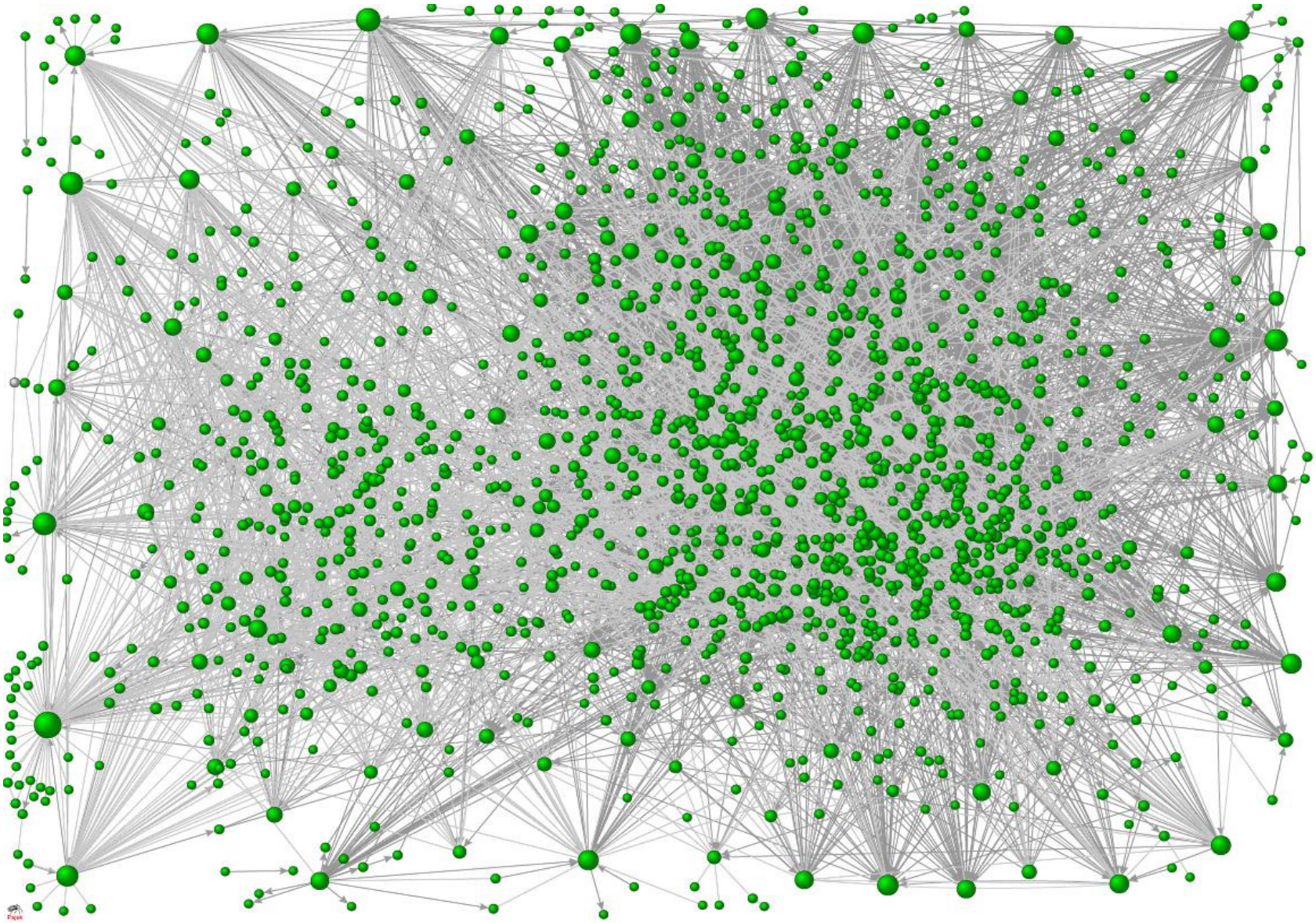
a **b**

Cancer signaling addiction: the most frequently used signaling events and cascades by cancer cells. Numbers represent mutation frequencies.

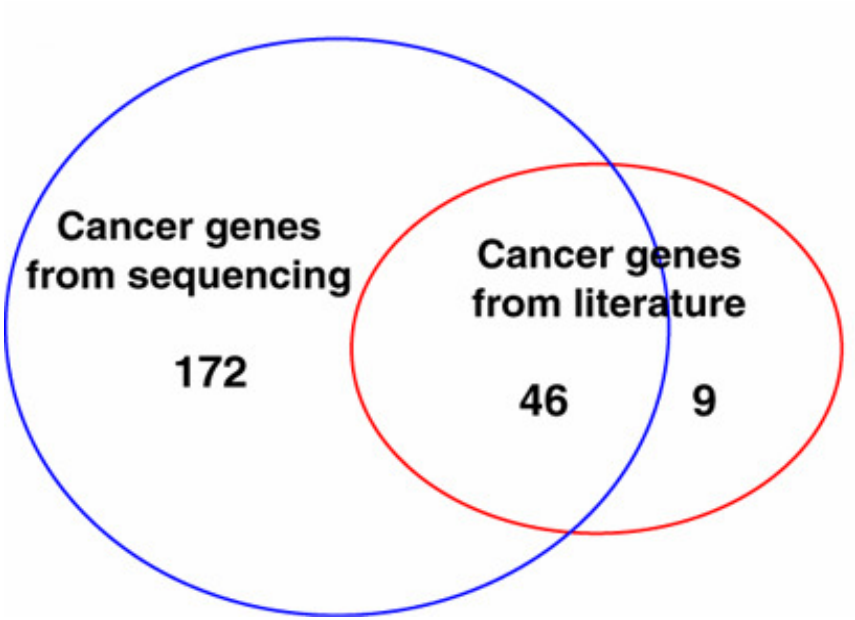
Datasets

- Analyzing the human signaling network by integrating 'cancer driver mutating' and cancer stem cell methylated silencing genes.
- Manually curation of a human cellular network (>1,600 proteins and >5,000 signaling relations), *Cui et al., Mol Syst Biol, 3:152, 2007.*
- Cancer stem cell methylated silencing genes (93 genes mapped onto the network), *Widschwendter et al., Nat Genet 39: 157, 2007; Schlesinger et al., Nat Genet 39: 232, 2007; Ohm et al., Nat Genet 39:237; 2007.*
- Cancer driver mutating genes (227 genes mapped onto the network), COSMIC database, literature curation and genome sequncing of tumors, *Thomas et al., Nat Genet 39: 347, 2007; Sjoblom et al., Science 314: 268, 2006.*

Human cellular signaling network



Tumor genome sequencing vs literature curation

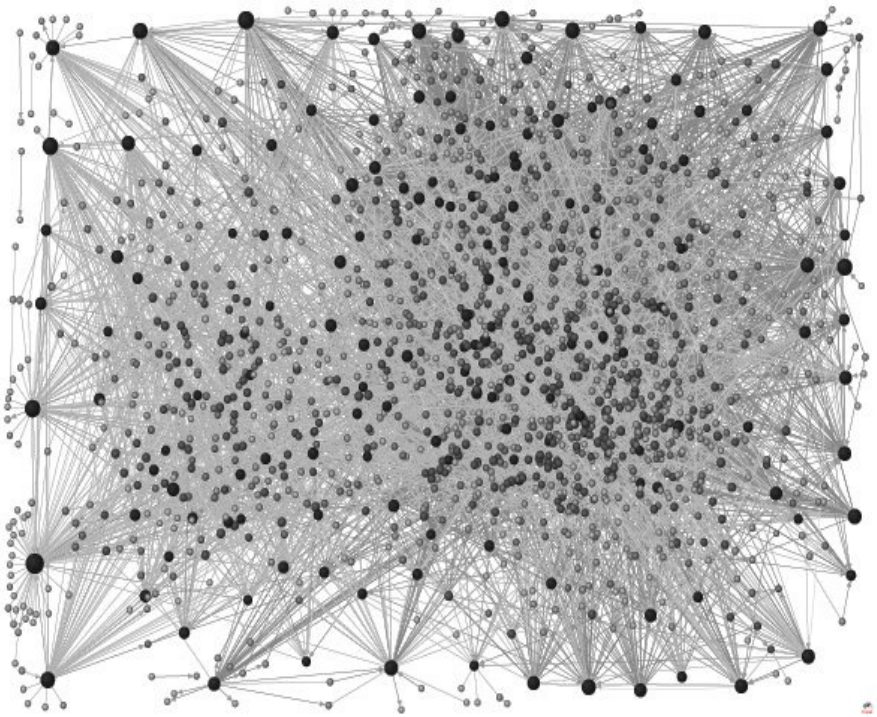


Driver mutating genes on the network, most of them have been determined from genome sequencing.

Questions addressed

- Where are the oncogenic stimuli (cancer mutating and methylated-silencing genes) embedded and distributed in the network architecture?

- What are the principles by which genetic and epigenetic alterations trigger oncogenic signaling events?

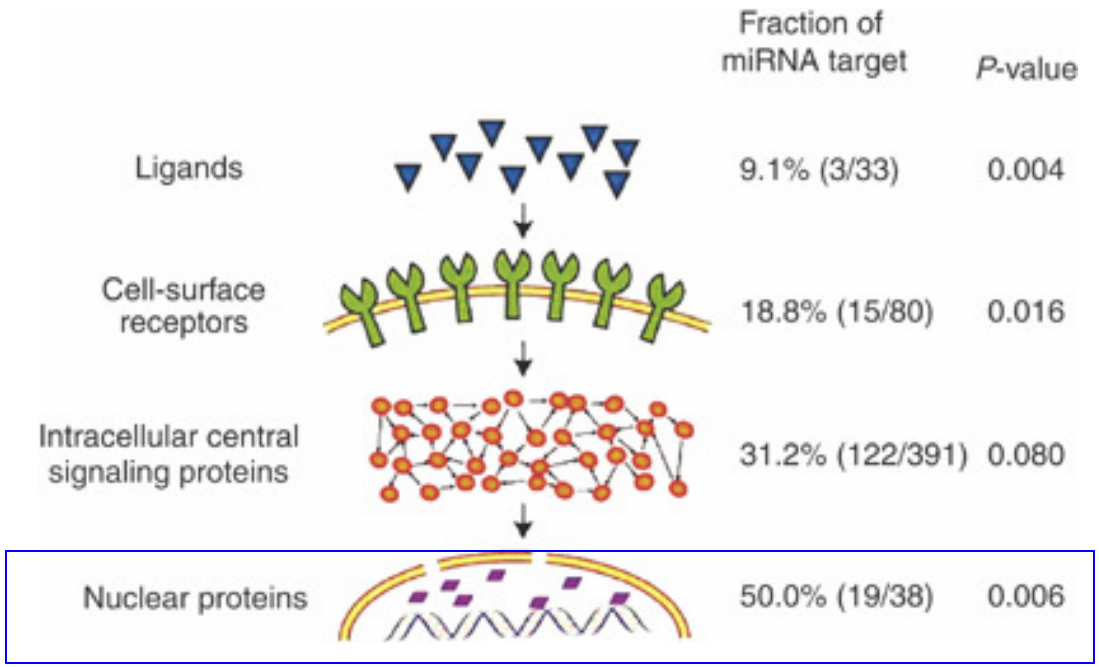


Output layer of the signaling network

- The downstream layer of the network is enriched with:

  - cancer driving mutating genes.
  - highly mutated genes.
  - microRNA-regulated genes.

- No such patterns for methylated-silencing genes.



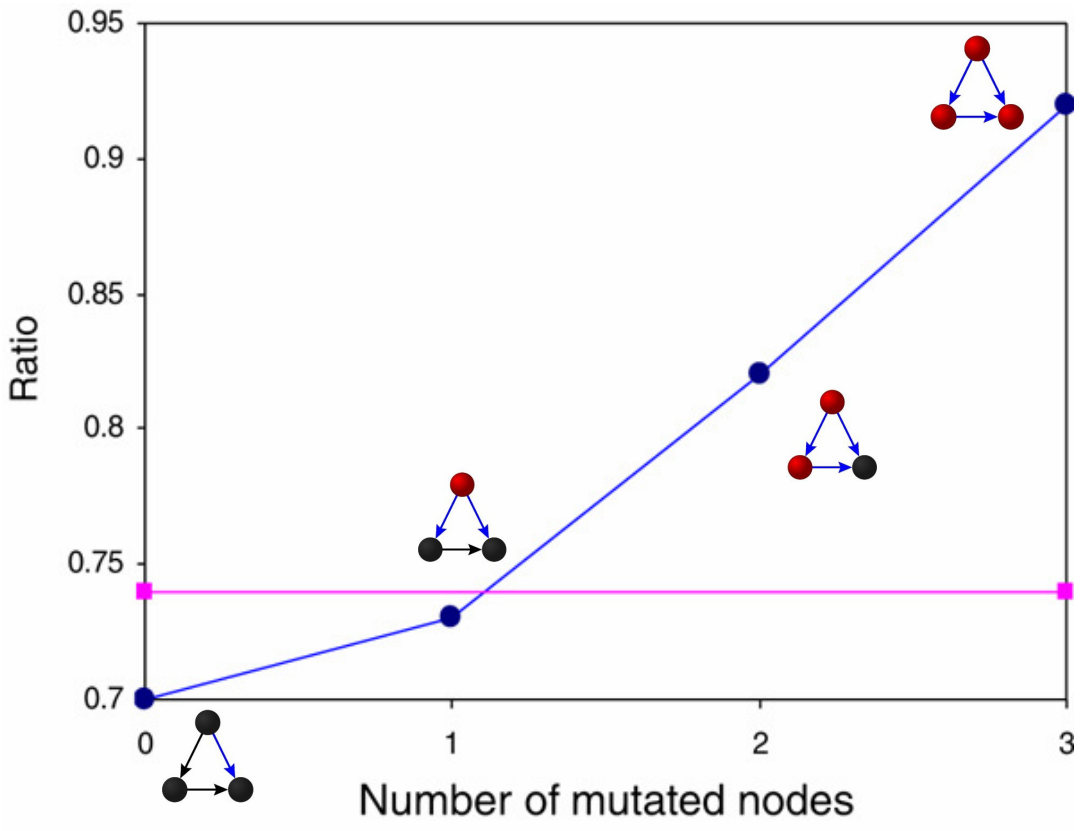
Cui et al., Mol Syst Biol 2: 46, 2006

Cui et al., Mol Syst Biol 3: 152, 2007

Awan et al., IET Syst Biol 1: 292, 2007

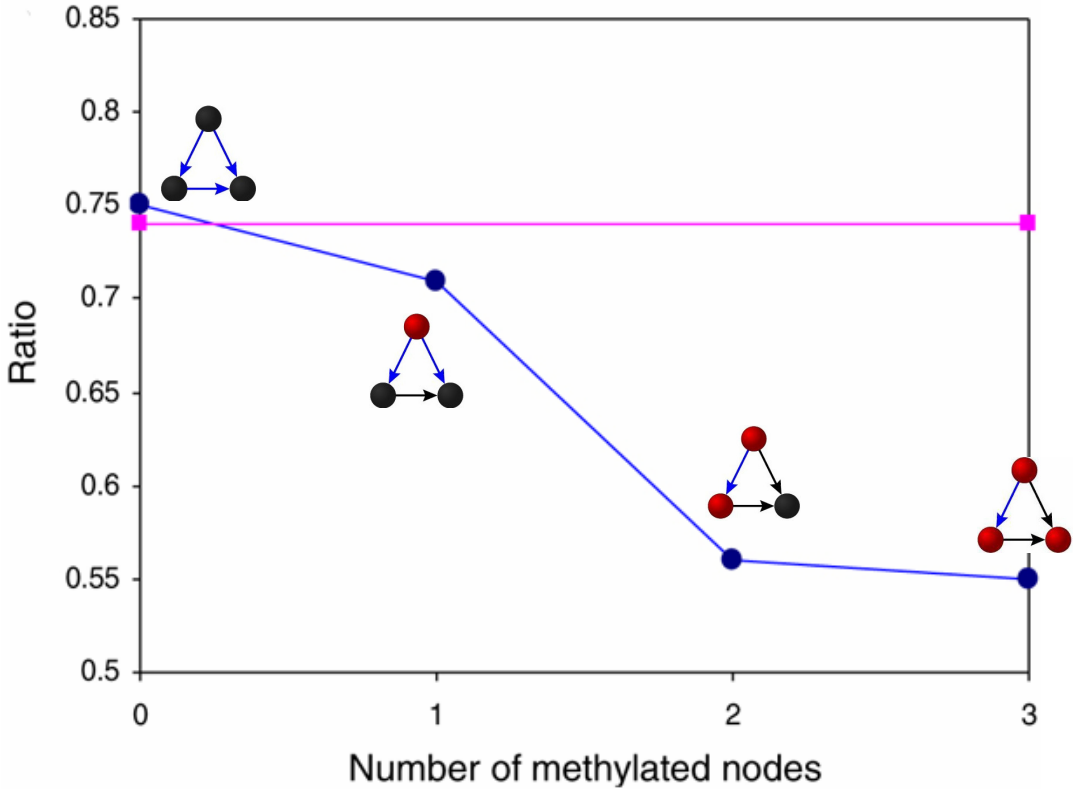
Mutating oncogenes and network motifs

- The more mutating nodes a motif has, the more positive links that motif has.
- Because the positive loops must constitutively activate downstream nodes, this pattern suggest that oncogene mutation results in gain-of-function of the mutants.
- Experimentally validated examples: PI3K in tumors, *Gymnopoulos et al., PNAS, 104: 5569, 2007.*



Methylated genes and network motifs

- The more methylated nodes a motif has, the less positive links that motif has.
- The mutated tumor suppressors share the same pattern.
- Gene silencing and tumor suppressor mutation could break the negative feedback loops.



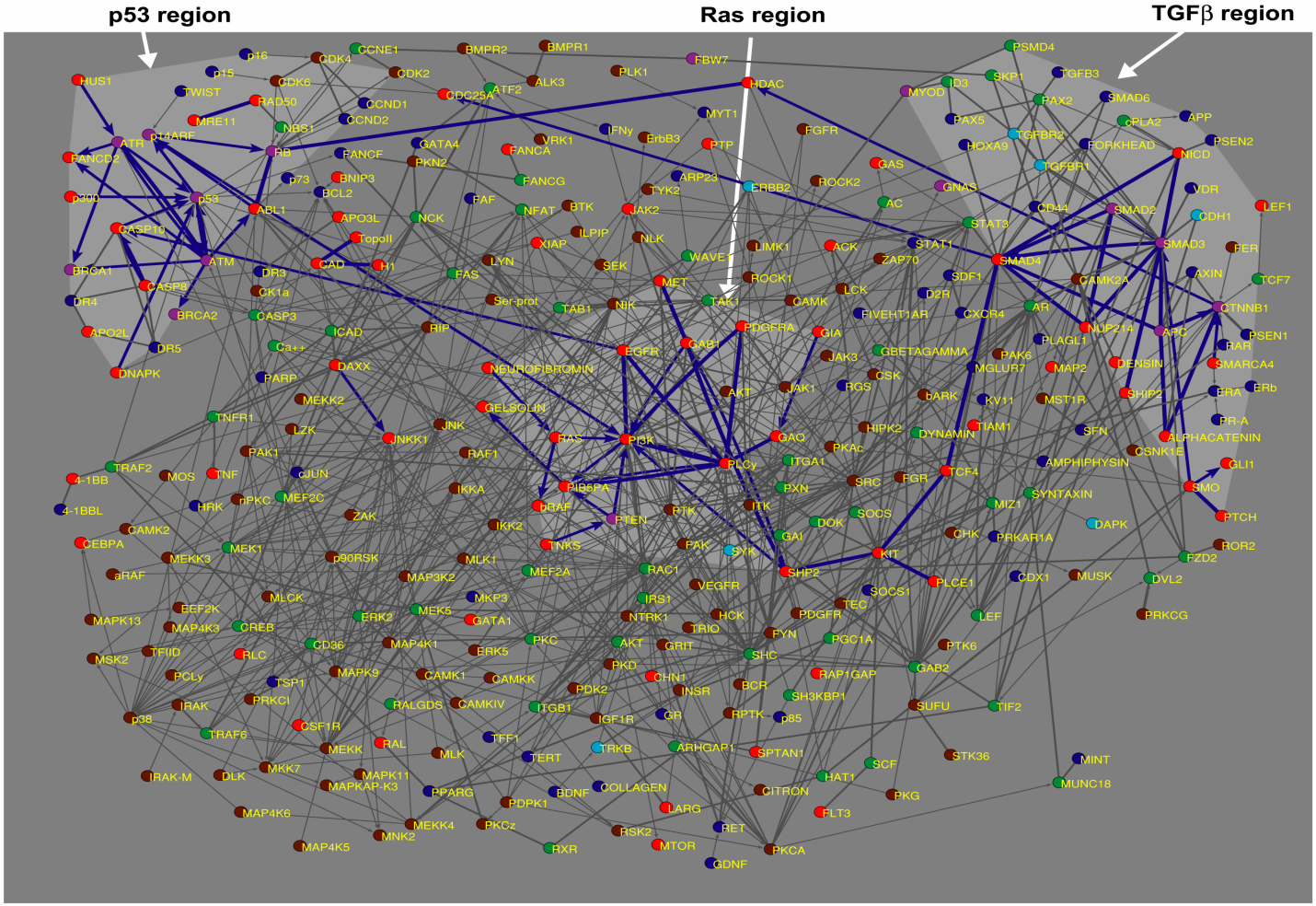
Questions addressed

- Given that so many genes have genetic and epigenetic aberrations in cancer signaling,
  - What is the architecture of cancer signaling?
  - Do any tumor-driven signaling events represent 'oncogenic addiction' (the phenomenon by which certain cancer cells become dependent on certain signaling cascades for growth or survival)?

Human cancer signaling map

Uncovered well-known cancer signaling events

Suggested many putative cancer signaling events

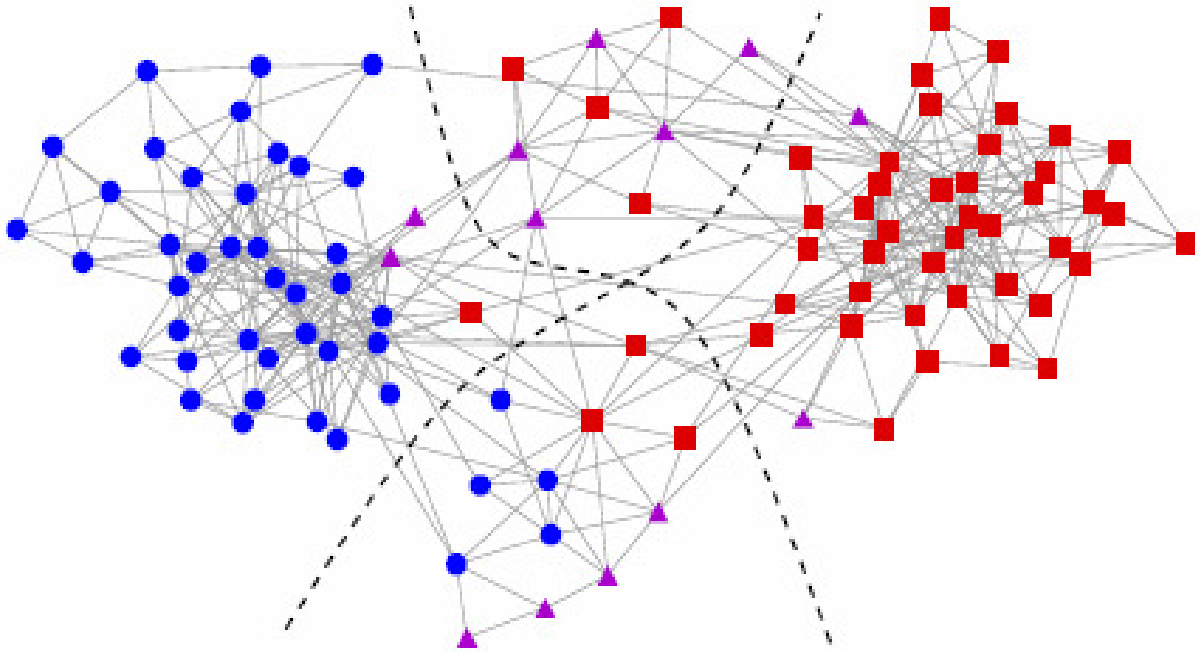


Almost ~10% of the genes are highly mutated and most frequently used by cancer cells, furthermore, they form 3 network regions (cancer signaling superhighways).

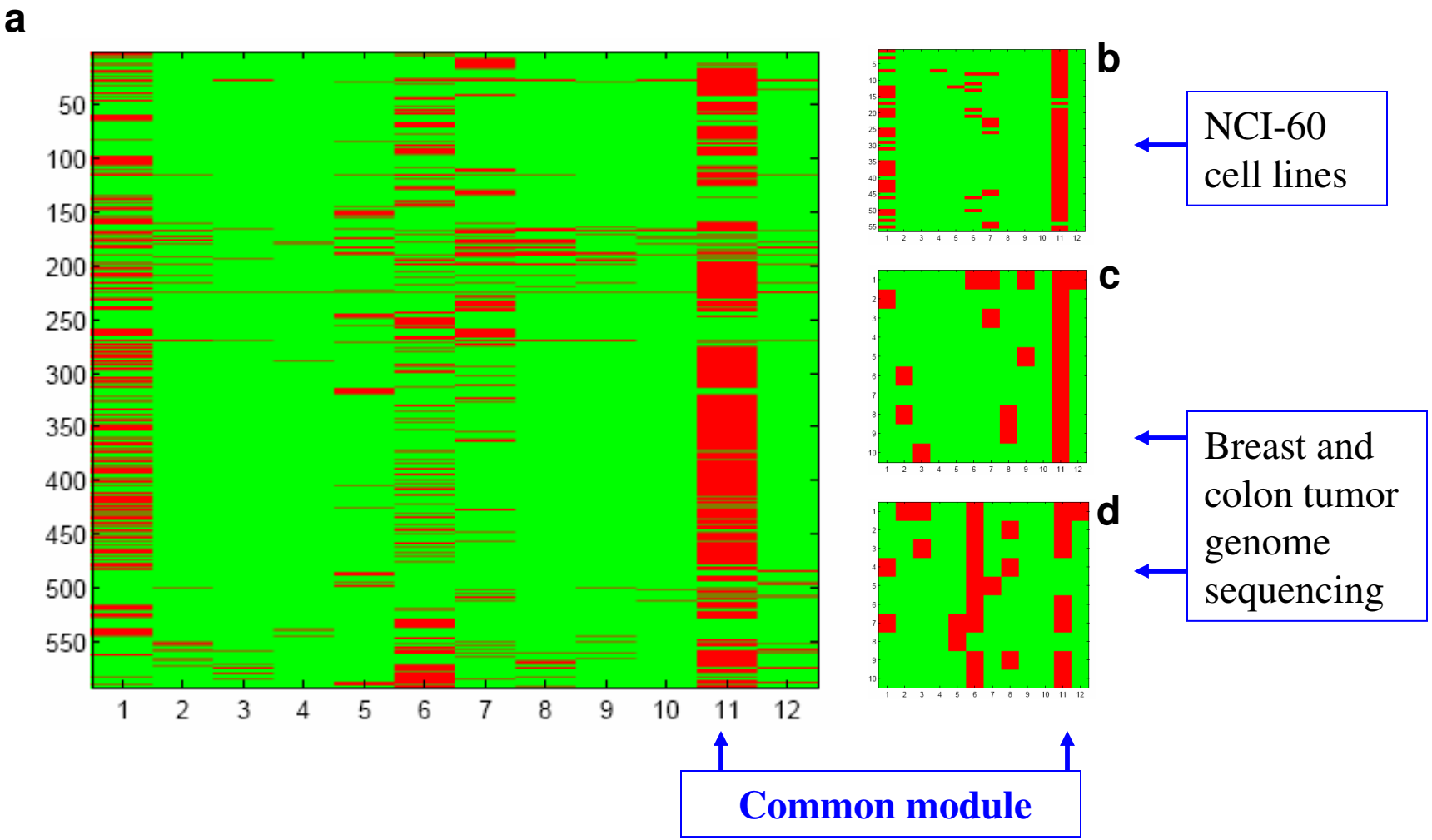
Questions addressed

- Given that so many genes have genetic and epigenetic aberrations in cancer signaling:
  - Who are the central players in oncogenic signaling?
  - Are there any signaling partnerships generally used to generate tumor phenotypes?

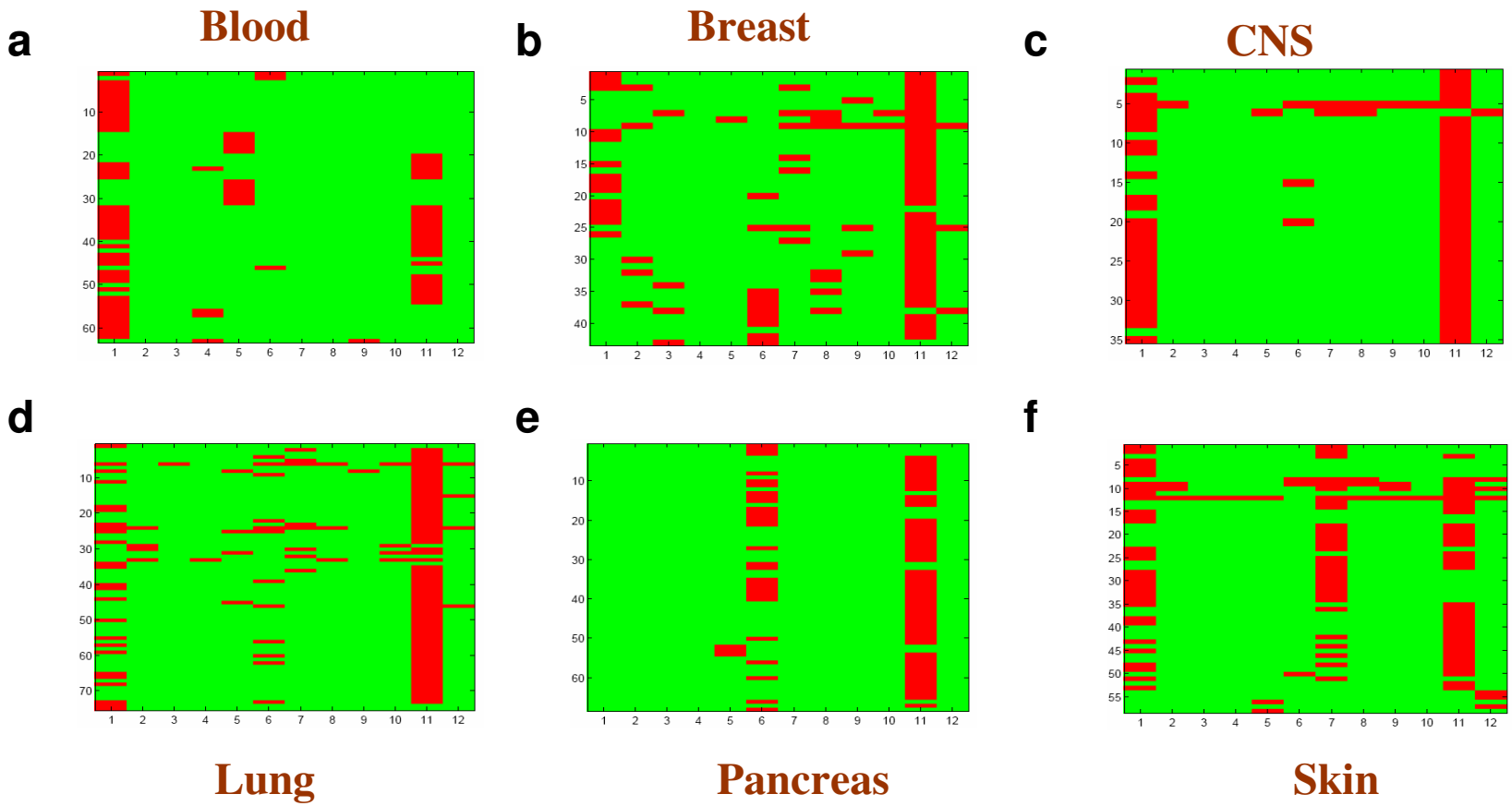
Network community



Collaboration of network communities in tumorigenesis



Representative cancer types



blood

1. Tumorigenesis: common module + tumor type specific modules.
2. Suggest that breast and lung cancers have more signaling mechanisms, therefore, more subtypes (true), easily occur than others (top cancer types in the world).

Challenge the current view of cancer signaling

- Signaling pathways and their collaborations driver cancer development and progression.
- However, almost all of the known signaling pathways can be charted by the “cancer driver mutating genes”.
- We dissected a few key protein communication modules, and showed that clear patterns of signaling module collaborations emerge recurrently in tumor samples.
- It represents the underlying ‘logic’ of cancer signaling and a more accurate view of how cancers originate.

Summary

- Provided a framework for discovering preferred combinations of signaling cascades used by cancer cells.
- Uncovered the underlying logic of cancer signaling: a protein communication module is predominantly used to collaborate with other modules (different for different types of cancer) in tumorigenesis and progression.
- Provided a framework for network analysis of the high-throughput genome sequencing of cancer and other disease samples.
- Details of this work: *Cui et al., A map of human cancer signaling, Mol Syst Biol, 3:152, 2007.*

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